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# SYNTHESIS OF 2'-DEOXY-5-FLUORO-5'-O-1",3",2"-OXAZAPHOSPHACYCLOHEXA-2"-YLURIDINE 2"-OXIDE AND RELATED COMPOUNDS

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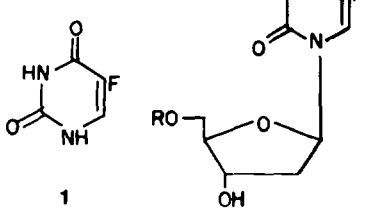
**Abstract**—*2',3'-O-Isopropylidene-5'-O-1",3",2"-oxazaphosphacyclohex-2"-yl-uridine 2"-oxide* has been obtained by the action of phosphoryl chloride and N-methylmorpholine, followed by 3-aminopropan-1-ol, on 2',3'-O-isopropylidineuridine. A similar reaction carried out on 3'-O-acetylthymidine, followed by removal of the acetyl group gave *5'-O-1",3",2"-oxazaphospha-2"-yl-thymidine 2"-oxide.* Both of these compounds were obtained more conveniently by treatment of 2',3'-O-isopropylideneuridine and thymidine respectively with 2-chloro-1,3,2-oxazaphosphacyclohexane 2-oxide in pyridine. Similar treatment of 2'-deoxy-5-fluorouridine gave *2'-deoxy-5-fluoro-5'-O-1",3",2"-oxazaphosphacyclohex-2"-yluridine 2"-oxide.* The latter compound was tested for activity against S 180 Crocker sarcoma and L 1210 mouse leukaemia. Only a marginal activity against the S 180 sarcoma was detected. However inactivity of the compound in inducing leukopenia indicated that it might be of low toxicity and that further testing of the compound would be justified.

5-Fluorouracil (**1**) is used as a chemotherapeutic agent in the treatment of certain malignant tumours.[1-3] Its mode of action is that it is converted *in vivo* into 2'-deoxy-5-fluorouridine 5'-phosphate (**2**), which acts as a powerful inhibitor of thymidylate synthetase, thus inhibiting the synthesis of DNA.[4] The chief disadvantages to the use of 5-fluorouracil are its toxicity to normal cells[2-5] and the development of resistance.[6,7] 2'-Deoxy-5-fluorouridine (**3**), although showing superior anticancer activity in some test systems, appears to have no advantages over 5-fluorouracil when used clinically.[3] This is probably due to its rapid metabolic breakdown to 5-fluorouracil.[8] The 5'-phosphate **2** is not an effective chemotherapeutic agent because it does not penetrate into cells in sufficiently high concentration.[4,9] Esters of **2** which might penetrate cells and then liberate the active agent, have been synthesised[10] but they do not appear to be useful clinically.

The present paper reports the synthesis of a derivative of 5-fluorouracil which might be expected to enter mammalian cells and to be converted metabolically into the active agent, **2**. The compound is 2'-deoxy-5-fluoro-5'-O-1", 3", 2"-oxazaphosphacyclohex - 2" - yluridine 2"-oxide (**4**).

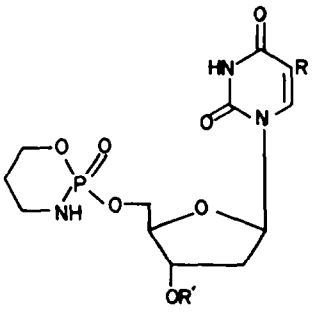


**1**

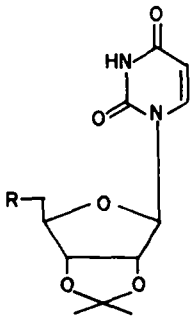


**2**: R = $(HO)_2P(O)$–
**3**: R = H
**7**: R = $H_2N$, O, HO

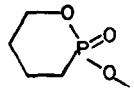
This was selected because the P-containing ring is the same as that which is present in the anticancer drug, cyclophosphamide (**5**). It is known that this drug is activated by metabolic oxidation and subsequent degradation to give the active alkylating agent **6** according to the following scheme.[11-13] A similar metabolic



**4**: R = F; R' = H
**10**: R = $CH_3$; R' = $COCH_3$
**11**: R = $CH_3$; R' = H



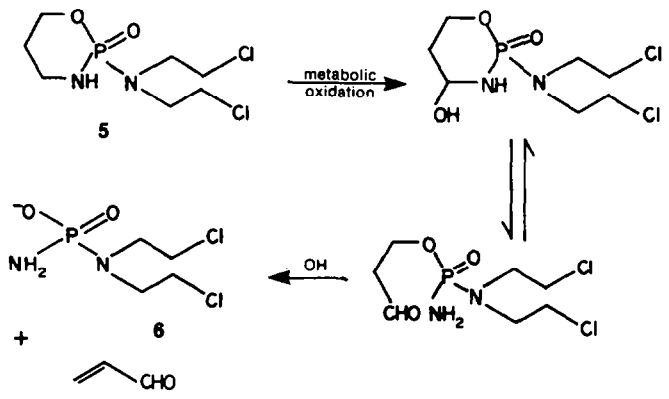
**8**: R =



**9**: R = Cl

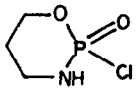
oxidation and degradation of **4** would lead to the phosphoramidate, **7**, which would then decompose to give **2**.

Investigations on the synthesis of compounds of this type were carried out initially on less expensive starting materials than 2'-deoxy-5-fluorouridine, namely 2',3' - O - isopropylideneuridine and thymidine. 2',3' - O - Isopropylideneuridine was treated with phosphoryl chloride in the presence of N-methylmorpholine until no starting material remained. 3 - Aminopropan - 1 - ol was then added to give the required product, 2',3' - O - isopropylidene - 5' - O - 1",3",2" - oxazaphosphacyclohex - 2" - yluridine 2"-oxide (**8**). A by-product of this reaction, which was produced in appreciable amount if the first stage of the reaction, namely the treatment with phosphoryl chloride was prolonged was 5' - chloro - 5' - deoxy - 2',3' - O - isopropylideneuridine (**9**). This reaction was then applied to thymidine in the hope of obtaining specific reaction at the 5' - O - position, but none of the required product was obtained. Instead, polymeric material, probably poly(thymidylic acid) was the major product. However, treatment of 3'-O-acetylthymidine in a similar manner gave the 1,3,2-oxazaphosphacyclohex-2-yl derivative, **10**, which upon treatment with




5 6

methanolic ammonia gave 5' - O - 1",3",2" - oxazaphosphacyclohex - 2" - ylthymidine 2"-oxide (**11**). This series of reactions was then carried out on 3' - O - acetyl - 2' - deoxy - 5 - fluorouridine. However, although the n.m.r. spectra indicated that the required product, **4** had been obtained the overall yield was only about 5% and the product was not obtained completely pure. The synthesis of these compounds by direct treatment of the nucleoside with 2 - chloro - 1,3,2 - oxazaphosphacyclohexane 2-oxide (**12**) was investigated.



**12**

Attempts to obtain compound **12** by the procedure described in the literature,[14] were unsuccessful, but a modification[15] gave a satisfactory product. Treatment of 2',3' - O - isopropylideneuridine with **12** in the presence of pyridine gave **8** which was identical with the product obtained by the previous route. The $^{31}P$ NMR spectrum of the compound gave two peaks ($\delta -3.96$ and $-3.83$ ppm) upon proton decoupling and it is thought that this may be due to the presence of diastereomers arising because of the chiral centre at P.

Thymidine was treated with **12** under similar conditions to give **11** in about 20% yield. The structure assigned to the product was confirmed by NMR spectroscopy. Thus the electron-withdrawing effect of the 5'-O-substituent is sufficient to shift the 5'-$CH_2$ and 4'-CH proton resonances from their normal positions of $\delta$ 3.55 and 3.75 respectively to the lower field region normally occupied solely by the 3'-CH resonance at $\delta$ 4.24. Because of this and also the 6"-$CH_2$ resonances, absorptions due to six protons appear in the $\delta$ 4.0–4.6 region of the spectrum. An absorption at $\delta$ 5.17, removed by the addition of $D_2O$, was ascribed to the 3'-OH group (*cf* 3'-OH of thymidine, $\delta$ 5.20). The $^{31}P$ NMR spectrum gave only one peak at $\delta$ 4.09 upon proton decoupling. It was not clear whether this was due to the preferential isolation of one diastereomer or whether the phosphorus resonances of the two diastereomers were fortuitously coincident.

Treatment of 2'-deoxy-5-fluorouridine with **12** under the same conditions as those described above gave 2' - deoxy - 5 - fluoro - 5' - O - 1",3",2" - oxazaphosphacyclohex - 2" - yluridine 2"-oxide (**4**) in 36% yield. In this case also the 5'-$CH_2$ proton resonance was shifted to lower field ($\delta \sim 4.3$) relative to those in 2' - deoxy - 5 - fluorouridine ($\delta$ 3.60) whereas the 3'-CH resonance was virtually unaffected. A signal due to the 3'-OH group ($\delta$ 5.22) was similar to that in 2'-deoxy-5-fluorouridine ($\delta$ 5.20). This signal was not present in the spectrum taken in deuteromethanol.

Compound **4** was tested for activity against S-180 Crocker sarcoma and L-1210 mouse leukaemia. In the latter the compound showed no activity and in the former only marginal activity at concentrations at which 5-fluorouracil was active. This lack of activity indicates that the compound was not being degraded to 5-fluorouracil by enzymic hydrolysis of the glycosidic linkage as occurs with the nucleotide, **2** or that the compound fails to penetrate cells. Lack of activity may also be due to the absence in the test systems of the enzymes necessary to oxidise the 1,3,2-oxazaphosphacyclohexane ring. However, compound **4** was also inactive in the leukopenia test at concentrations at which 5-fluorouracil was active. As this indicates the possibility of low toxicity, further testing of the compound is justified.

## EXPERIMENTAL

NMR spectra were recorded at 100 MHz. Tlc was carried out on silica gel (MN Kieselgel G/$UV_{254}$) and column chromatography on silica gel (Kieselgel 60, 70–120 mesh ASTM, type 7734), both supplied by E. Merck AG., Darmstadt, W. Germany.

2 - *Chloro* - 1,3,2, - *oxazaphosphacyclohexane 2-oxide.*[15] $POCl_3$ (76.7 g, 0.5 mole) was dissolveed in dry $CHCl_3$ (400 ml) and the soln cooled to $-15°$. A soln of 3-aminopropan-1-ol (37.5 g, 0.5 mole) in dry $CHCl_3$ (100 ml) containing $Et_3N$ (70 ml) was added dropwise with stirring to the mixture which was kept at $-10°$, followed by the addition of a further quantity (70 ml) of $Et_3N$ in dry $CHCl_3$ (100 ml), the temp being kept below 0°. The mixture was then maintained at 0° for 18 hr and the solvent removed under reduced pressure at 35°. The solid residue was extracted with dry acetone (4 × 200 ml), the acetone extract evaporated to dryness and to the residue there was added dry $CHCl_3$ (100 ml) and then $CCl_4$ (400 ml). Trituration of the mixture gave a crystalline solid which was filtered off and dried to give 2 - chloro - 1,3,2 - oxazaphosphacyclohexane 2-oxide (38 g. 49% yield), m.p. 80° (lit.[14] 80–83°) (Found: C, 23.3; H, 4.41; N, 8.84. 'Calc. for $C_7H_7ClNO_2P$: C, 23.2; H, 4.54; N, 9.01%). NMR $^1H$ $\delta$ ($CDCl_3$) 1.4–2.6 (2H, m, H-5), 3.0–3.7 (2H, m, H-4), 4.16–4.85 ppm (3H, m, H-6, NH); $^{31}P$, $\delta$ ($CDCl_3$)-10.80 ppm. *m/e*, 157, 155 ($M^+$); 130, 128; 120; 92; 56 (Base Peak).

*Reaction of 2',3'-isopropylideneuridine with phosphorylchloride and 3-aminopropan-1-ol*

A soln of 2',3'-O-isopropylideneuridine (1.13 g, 4 mmole) in 1,2-dimethoxyethane (25 ml) and N-methylmorpholine (0.4 ml) was added at 0° over 1 hr to a soln of $POCl_3$ (0.5 ml, 5.4 mmole) in 1,2-dimethoxyethane (10 ml) and N-methylmorpholine (0.4 ml). The mixture was stirred at $\sim 20°$ for 18 hr (tlc of a sample in

$CHCl_3$–EtOH (9:1) showed that nearly all of the isopropylideneuridine had disappeared and that a major component, which remained on the base line and a faster-running component, were present) and then 3-aminopropan-1-ol (0.5 g, 6.7 mmole) in 1,2-dimethoxyethane (10 ml) and N-methylmorpholine (2 ml) were added at 0° over 15 min. The mixture was allowed to warm up to ~20° and stirring continued for 24 hr (tlc of the mixture in $CHCl_3$–EtOH (9:1) showed the presence of four components of $R_f$ 0.23, 0.36 (2',3'-O-isopropylideneuridine), 0.65 (minor) and 0.74). The mixture was evaporated to dryness and the residue dissolved in $CHCl_3$ and fractionated on a column of silica gel (150 g). Elution with $CHCl_3$ gave the components of $R_f$ 0.74 and 0.65 separately and subsequent elution with $CHCl_3$–EtOH (9:1) separated the 2',3'-O-isopropylideneuridine and the fraction of $R_f$ 0.23. The fractions containing the component of $R_f$ 0.74 were pooled and evaporated to dryness to give a solid (400 mg) which upon crystallisation from EtOH gave 5' - chloro - 5' - deoxy - 2',3' - O - isopropylideneuridine (190 mg), m.p. 166–167° (Found: C, 47.9; H, 4.90; Cl, 12.0; N, 9.30. Calc. for $C_{12}H_{15}ClN_2O_5$: C, 47.6; H, 4.99; Cl, 11.7; N, 9.25%), $\lambda_{max}$ 262 nm ($\epsilon$, 10, 100) at pH 7: $\delta$ ($CDCl_3$) 1.34 (3H, s, $-CH_3$), 1.56 (3H, s, $-CH_3$), 3.76 (2H, m, H-5'), 4.36 (1H, m, H-4'), 4.94 (2H, m, H-2', H-3'), 5.68 (1H, d, H-5), 5.74 (1H, d, H-1'), 7.32 (1H, d, H-6), 9.73 ppm (1H, bs, -NH). The fractions containing the component of $R_f$ 0.23 were shown by NMR spectroscopy to contain the required product, but it proved difficult to isolate. To obtain it the procedure described above was modified so that the treatment with $POCl_3$ was reduced from 18 hr to 3 hr and the reaction with 3-aminopropanol increased from 24 hr to 64 hr. The mixture was then worked up as described above. The fractions containing the component of $R_f$ 0.23 was combined and evaporated to dryness to give *2',3' - O - isopropylidine - 5' - O - 1",3",2" - oxazaphosphacyclo hex-2" - yluridine 2"-oxide* as a white solid (415 mg) (Found: C, 45.0; H, 5.60; N, 10.5. $C_{15}H_{22}H_3O_8P$: requires C, 44.7 H, 5.50; N, 10.4%) which was chromatographically identical to the compound prepared as described below.

*2',3' - O - Isopropylidene - 5' - O - 1",3",2" - oxazaphosphacyclohex - 2" - yluridine 2" - oxide*

To a mixture of 2',3 - O - isopropylideneuridine (0.711 g, 2.5 mmole) and 2 - chloro - 1,3,2 - oxazaphosphacyclohexane 2-oxide (0.78 g, 5 mmole) there was added dry pyridine (50 ml) and the mixture stirred at ~20° for 18 hr. The pyridine was then removed by evaporation under reduced pressure followed by coevaporation with MeOH. The residue was dissolved in $CHCl_3$ and fractionated on a column of silica gel (200 g) using $CHCl_3$–MeOH (9.1) as the eluant. The fractions containing the required material were collected, the solvents removed under reduced pressure and the residue crystallised from $CHCl_3$-light petroleum to give the *title compound* (52 mg) (Found: C, 44.6; H. 5.50. $C_{12}H_{22}N_3O_8P$: requires C, 44.7; H, 5.50%); $\lambda_{max}$ 262 nm ($\epsilon$, 9,500), $\lambda_{min}$ 232 nm ($\epsilon$, 2,430) in EtOH; NMR $^1H$, $\delta$ [$(CD_3)_2SO$] 1.30 (3H, s, $-CH_3$), 1.49 (3H, s, $-CH_3$), 1.50–1.80 (2H, m, H-5"), 3.00 (2H, m, H-4"), 4.00–4.30 (5H, m, H-4', H-5', H-6"), 4.80 (1H, m, H-3'), 5.0 (1H, m, H-2'), 5.62 (1H, d, H-5, J = 8 Hz), 5.80 (1H, d, H-1') 7.32 (1H, bs, -NH-3"), 7.72 (1H, d, H-6, J=8 Hz), 11.35 ppm (1H, s, -NH-3); $^{31}P$, $\delta$ [$(CD_3)_2SO$] – 3.96, – 3.83 ppm; *m/e* 404, 403 ($M^+$), 388, 292, 251, 191, 138 (Base peak), 120.

*3' - O - Acetyl - 5' - O - 1",3"2" - oxazaphosphacyclohex - 2" - ylthymidine 2" - oxide.* To a stirred soln of $POCl_3$ (1 ml, 10.8 mmole) and N-methylmorpholine (0.9 ml) in 1,2-dimethoxyethane (20 ml) there was added at 0° over 30 min a soln of 3'-O-acetylthymidine (2.27 g, 8 mmole) and N-methylmorpholine (0.6 ml) in 1,2-dimethoxyethane (40 ml). The mixture was allowed to reach ~20° and the stirring continued for a further 3 hr. It was then cooled to 0° and a soln of 3 - aminopropan - 1 - ol (0.99 g, 13 mmole) and N-methylmorpholine (2 ml) in 1,2-dimethoxyethane (25 ml) added with stirring over 15 min. The mixture was allowed to warm up to ~20° and the stirring continued for 18 hr [tlc of the mixture in $CHCl_3$–EtOH (9.1) showed the presence of 3'-O-acetylthymidine ($R_f$ 0.32), the required product ($R_f$ 0.41) and two other components ($R_f$ 0.28 and 0.60)]. The mixture was filtered and the filtrate evaporated under reduced pressure to give a residue which was fractionated by chromatography on silica gel (500 g). The required product was eluted with $CHCl_3$–EtOH (19.1). Evaporation of the solvent gave a white solid which was crystallised from EtOH–$CHCl_3$ to give *3' - O - acetyl - 5' - O - 1",3",2" - oxazaphosphacyclohex - 2" - ylthymidine 2"-oxide* (380 mg) (Found: C, 44.4; H, 5.70; N, 10.0. $C_{15}H_{22}N_3O_8P$ requires: C, 44.7; H, 5.50; N, 10.4%); $\lambda_{max}$ 267 nm ($\epsilon$, 9,390), $\lambda_{min}$ 233 nm ($\epsilon$, 1,700) in EtOH; $\delta$[$(CD_3)_2SO$] 1.81 (2H, m, H-5"), 1.91 (3H, s, $-CH_3$), 2.08 (3H, s, $-COCH_3$), 2.35 (2H, m, H-2'), 3.20 (2H, m, H-4"), 4.25 (4H, m, H-5', H-6"), 4.40 (1H, m, H-4'), 5.35 (1H, m, H-3'), 6.35 (1H, t, H-1'), 7.55 (1H, s, H-6), 9.60 ppm (1H, s, -NH-3).

*5' - O - 1",3"2" - Oxazaphosphacyclohex - 2" - ylthymidine 2"-oxide*

(a) A solution of the foregoing compound (160 mg) in MeOH-aqueous ammonia (sp.g. 0.88; 1:1; 10 ml) was kept at ~20° for 18 hr (tlc in $CHCl_3$–EtOH (9:1) showed the absence of starting material and the presence of a slower-running component and traces of two faster-running components). The solvent was removed under reduced pressure to give a white solid (150 mg). This was purified by preparative tlc and the appropriate component isolated and crystallised from EtOH to give *the title compound* (40 mg), m.p. 177–185 (Found: C, 43.3; H, 5.90; N, 11.9. $C_{13}H_{20}N_3O_7P$ requires C, 43.2; H, 5.60; N, 11.6%); $\lambda_{max}$ 267 nm ($\epsilon$, 9,710), $\lambda_{min}$ 234 nm ($\epsilon$, 2,650) in ethanol; $\delta$[$(CD_3)_2SO$] 1.73 (2H, m, H-5"), 1.75 (3H, s, $-CH_3$), 2.13 (2H, t, H-2'), 3.28 (2H, m, H-4"), 3.60 (1H, s, NH-3"), 3.96–4.30 (6H, m, H-3', H-4', H-5', H-6"), 5.19 (1H, s, OH-3'), 6.20 (1H, t, H-1'), 7.53 (1H, s, H-6), 11.2 ppm (1H, s, NH-3).

(b) To a mixture of thymidine (2.42 g, 10 mmole) and 2-chloro-1, 3,2-oxazaphosphacyclohexane 2-oxide (1.56 g, 10 mmole) there was added dry pyridine (20 ml) and the mixture stirred at ~20° for 20 hr. The pyridine was removed by evaporation under reduced pressure followed by co-evaporation with MeOH. The residue was purified by chromatography on silica gel (600 g) using $CHCl_3$–EtOH (3:1) as eluant and further purification on second column using EtOAc–EtOH (3:1) as eluant. The relevant fractions were pooled and evaporated to dryness to give *the title compound* (800 mg) as an amorphous powder which upon crystallisation from EtOH gave a product of m.p. 185–193° (Found: C, 43.2; H, 5.64; N, 11.6. Calc. for $C_{13}H_{20}N_3O_7P$: C, 43.2, H, 5.60; N, 11.6%); $\lambda_{max}$ 267 nm, ($\epsilon$, 9,870), $\lambda_{min}$ 233 nm ($\epsilon$, 2,460) in ethanol. NMR $^1H$, $\delta$ ($CD_3OD$) 1.70 (2H, m, H-5"), 1.90 (3H, s, $-CH_3$), 2.25 (2H, t, H-2'), 3.00–3.40 (2H, m, H-4"), 3.75 (1H, bs, -NH-3"), 4.00–4.60 (6H, m, H-3', H-4', H-5', H-6"), 5.17 (1H, s, -OH-3'), 6.25 (1H, t, H-1'), 7.55 ppm (1H, s, H-6); $^{31}P$, $\delta$ [$(CD_3)_2SO$] – 4.09 ppm. *m/e* 361 ($M^+$), 236, 218, 138, 126 117 (Base peak), 99, 81.

*2' - Deoxy - 5 - fluoro - 5' - O - 1",3",2" - oxazaphosphacyclohex - 2" - yluridine 2" - oxide.* 2' - Deoxy - 5 - fluorouridine (2.46 g, 10 mmole) was treated with 2 - chloro - 1,3,2 - oxazaphosphacyclohexane 2-oxide (1.56 g, 10 mmole) in pyridine in a similar manner to that described above. The product was isolated by chromatography on silica gel using EtOAc–EtOH (3:1) as eluant. The eluate was evaporated to dryness to give *the title compound* as an amorphous powder (1.3 g) which was crystallised from EtOH and then from propan-2-ol, m.p. 105° (Found: C, 40.6; H, 5.53; N, 10.3 $C_{12}H_{17}FN_3O_7P.C_2H_5OH$ requires: C, 40.9; H, 5.63; N, 10.2%) (The presence of EtOH is confirmed by the NMR spectrum); $\lambda_{max}$ 270 nm ($\epsilon$, 8,230), $\lambda_{min}$ 237 nm ($\epsilon$, 1,720) at pH 7. $\delta$($CD_3OD$) 1.10 (3H, t, $CH_3CH_2OH$), 1.77 (2H, m, H-5"), 2.30 (2H, m, H-2'), 3.10–3.58 (2H, m, H-4"), 3.55 (2H, q, $CH_3CH_2OH$), 4.00–4.54 (6H, m, H-3', H-4', H-5', H-6"), 6.27 (1H, t, H-1'), 7.96 (1H, d, H-6, J = 6.5 Hz); $\delta$ [$(CD_3)_2SO$, sample not crystallised from ethanol] 1.75 (2H, m, H-5"), 2.18 (2H, m, H-2'), 3.46 (2H, m, H-4"), 3.88 (5H, bm, H-4', H-5', H-6"), 4.20 (1H, m, H-3'), 5.22 (1H, bs, OH-3'), 6.18 (1H, m, H-1'), 7.78 (1H, d, H-6, J = 7Hz). *m/e* 236, 180, 138, 130 (Base peak), 120, 110, 87, 81.

*Biological tests.* These were carried out in the laboratories of Hoffman-La Roche, Basle. Compound 4 was tested against S-180 Crocker sarcoma at 100 mg/Kg. The ratio, tumour weight of controls/tumour weight of test was 2.0. This represents marginal activity. When the compound was tested against L-1210 mouse leukaemia at 50 mg/Kg there was no increase in the survival time

of the animals. The compound showed no activity in the leukopenia test at 100 mg/Kg.

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